Future trials aiming at patient selection outcomes will need usable tissue from almost all patients, as well as a protocol design and statistical plans that can accommodate the evolution of science during the life of the trial. Patients entering trials are generally prepared to consent to tissue sampling after an appropriate discussion with their treating physician. Most patients seem willing to allow diagnostic biopsy tissues to be used for research, but obtaining biopsies purely for research purposes is more challenging. Ethics boards may object to banking of tissues for future undefined studies and focusing on the pathways of interest, and careful consideration to the wording of the informed consent can be very helpful in this regard. What is clear is that this is a rapidly moving and important field and consultation between academia, industry, regulators, ethics boards, patient advocates and patients themselves is going to be key to improving the acquisition of samples for future biomarker research, ultimately leading to better targeted therapies.

CONFLICT OF INTEREST STATEMENT: Dr. N. Botwood M.D. is employed by AstraZeneca, Pharmacueticals Division in Clinical Research & Development. There is no conflict of interest involved with any matters presented in this paper.

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VALIDATION OF MULTIPLE BIOMARKERS: REGULATORY EXPECTATIONS

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The speaker offered his personal viewpoint on validation of multiple biomarkers. Pharmaco-dynamic biomarkers have a role in exploratory trials as markers of response and as proof of concept for demonstrating drug activity. They can help establish the dose–activity relationship in classical dose finding or phase II studies. In exploratory trials, pharmacodynamic biomarkers may serve as indicators of anti-tumour activity or as predictors of activity/tolerance for future screening in confirmatory trials. Confirmatory trials may rely on biomarkers for qualitative screening to determine which treatment is most appropriate for which patients, or to indicate efficacy and safety. Biomarkers can also be used in quantitative screening to establish dosing or as surrogate end-points to evaluate clinical benefit or harm. Because of their importance in selecting patient populations and their relevance in clinical trials of molecularly targeted agents, however, biomarkers must be detected, selected and validated.

Biomarkers are more useful from a regulatory standpoint if they have a biologically plausible basis, at least in theory. Regulators also prefer biomarkers that give dichotomous answers (e.g. yes/no; positive/negative) rather than relying on a semiquantitative grading scale. Though in some cases, it is possible to transform semiquantitative scores to binary ones. In any event, developers and investigators should always keep in mind multiple pathways, time-related variability and inter-tumour differences.

Pharmacodynamic markers relate to effects that can be observed through biology, biochemistry or imaging. They should reflect an expected change related to the tested agent's mechanism of action. For example, reduced tumour blood flow by anti-angiogenic agents, increased apoptosis by pro-apoptotic agents, or changes in early or late effectors of a signal-induction pathway (e.g. phosphorylation of a receptor leading to the inhibition of an initiation factor). Pharmacodynamic markers should demonstrate an effect on representative tissues (e.g. skin or oral mucosa in the case of inhibitors of endothelial growth factor receptor). It was emphasised that to regulators, it is not acceptable to define a pharmacodynamic marker and use it for validation in the same study.

Biomarkers can be an indicator of efficacy as a surrogate marker but cannot serve as a marker of clinical benefit *per se*. Ideally, validation should be done prospectively, although initially, retrospective studies may be undertaken to identify surrogate markers. Circular validation is not acceptable as it would include using individuals identified as biomarker-positive at interim analysis in the final validation analysis. Validation should be done in another, complementary population that does not include the original subpopulation found to be positive for the biomarker.

In another scenario it is possible that treatment does not have a significant effect on overall survival in the entire population, but a survival advantage is found among those who have a specific biomarker. Such a scenario might be acceptable for registration or licensure of the anticancer agent if the subpopulation were pre-specified and if the difference in outcomes between the two groups (biomarker-positive and -negative) was clear-cut. In principle, regulatory authorities might want to avoid registering products that offer a benefit in overall survival only for the biomarker-positive subpopulation. The difference between the treatment's effects on those with and without the biomarker would have to be very clear.

Several definitions of surrogate end-point exist. According to the Biomarkers Definitions Working Group, it is 'a biomarker that

is intended to substitute for a clinical end-point and is expected to predict clinical benefit (or harm or lack of clinical benefit) based on epidemiologic, therapeutic, pathophysiologic, or other scientific evidence'.[1] According to Fleming et al., 'Any changes induced in the surrogate end-point by a treatment must accurately reflect changes in the true end-point'.[2] Prentice et al. clarify that a surrogate end-point is 'a response variable for which a test of the null hypothesis of no relationship to the treatment groups under comparison is also a valid test of the corresponding null hypothesis based on the true end-point'.[3]

Surrogate markers are quantitatively related to tumour burden in all sites. Ideally, they should not be affected by subclonal heterogeneity, and they should be assessable even at low tumour burdens.

Surrogate markers are quantitatively related to tumour burden in all sites. Ideally, they should not be affected by subclonal heterogeneity, and they should be assessable even at low tumour burdens. When selecting possible surrogate markers as clinical trial end-points, investigators should weigh several important criteria in order to collect data that will be relevant and sufficient for subsequent licensure or registration of the anticancer agent. First, is the potential surrogate biologically associated with the true end-point? Second, is the treatment somehow associated with the potential surrogate end-point? Third, does the potential surrogate mediate the treatment's effect on the true end-point and is the potential surrogate biologically associated with the true end-point?[4]

Under some circumstances the use of a surrogate end-point might be misleading. For example, even with known perfect correlation within randomized groups, one cannot rely on the potential surrogate end-point for valid inference about the true end-point, because even the direction of their effects could be opposite.[5] Thus, even in preliminary trials, investigators should not base conclusions on potential surrogate end-points if the validation is based solely on high correlation with the true end-point.

In conclusion, we must agree on new rules that will allow us to accept biomarkers at early stages of new drug investigations. These biomarkers must correspond with some clinically relevant measure, and their use must comply with the usual statistical tools acceptable for new drug registration or licensure. The best sort of trial to select and validate surrogate end-points is a comparative prospective trial that (1) determines the mean difference and variance in the surrogate when the experimental and reference groups are compared, and (2) predicts the mean difference and variance in the ideal true end-point when the experimental and reference groups are compared. Such a trial might not save time or spare patients, however, compared with a trial based on conventional end-points.

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BIOMARKERS: TRANSLATION INTO LABELLING LANGUAGE

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Drug development has progressed to the age of individualisation. Therefore opportunities exist for applying biomarkers in this new paradigm. Several definitions of relevant terms have been proposed by the Biomarkers Definitions Working Group of the National Institutes of Health (NIH) and the U.S. Food and Drug Administration (FDA):

- A biological marker (biomarker) is 'a characteristic that is objectively measured and evaluated as an indicator of normal biological processes, pathogenic processes, or pharmacologic responses to a therapeutic intervention'.[3]
- A clinical end-point is 'a characteristic or variable that reflects how a patient feels, functions or survives'.[3]
- A surrogate end-point[4] is 'a biomarker that is intended to substitute for a clinical end-point. A surrogate end-point is expected to predict clinical benefit or harm (or lack of benefit or harm) based on epidemiologic, therapeutic, pathophysiologic, or other scientific evidence . . .Although all surrogate end-points can be considered biomarkers, it is likely that only a few biomarkers will achieve surrogate end-point status'.[3]

Pharmaceutical manufacturers, clinical investigators, and regulators rely on different types of biomarkers in the context of drug development. *Diagnostic biomarkers* provide the means to define a population with a specific disease. *Prognostic biomarkers* correlate with outcomes. For example, over expression of her-2/neu in breast cancer or epidermal growth factor receptor (EGFR) expression in colorectal cancer indicates poor prognoses. In addition, tumour size, often assessed with radiographic tools, is a prognostic marker because it correlates with outcome. Such prognostic markers are frequently the basis for establishing inclusion criteria for a clinical trial or for defining a patient population. Predictive biomarkers define populations that might respond more favourably to a particular intervention from an efficacy or safety perspective. They can be used to stratify patients for subgroup analyses. *Surrogates* are biomarkers that correlate with clinical benefit and changes in the marker correlate with alterations in